REMARKS/ARGUMENTS

Claims 6-13, 15, 24, 32-38, 42, 49, 50, 56-61, 67, 68, and 70 have been canceled without acquiescence to any rejection of record and without prejudice for representation in a continuing application.

Claims 14 and 23 as well as 69 have been revised to include the feature of a method related to aromatase inhibitors, such as letrozole. The revisions better tailor the claims for currently contemplated business considerations and so are not made in acquiescence to any rejection of record. The claims have also been revised to use alternative language to more explicitly recite features that are inherent to the claims as previously presented. Applicants expressly reserve the right to re-present the subject matter of the claims in their previous form in a continuing application.

Support for the revisions is provided at least by paragraph [0040] of the instant application as published in US 2005/0239083.

Dependent Claim 16 and 25 have been revised to correspond to changes in Claims 14 and 23.

Dependent Claims 52-55 have been revised to correspond to revised Claims 14 and 23.

New Claims 71-73 have been introduced and are supported as explained above.

No new matter has been introduced, and entry of the above amendments is respectfully requested.

Claim objections

Claims 12, 35, 59, and 67-70 were objected to as containing various informalities. Applicants respectfully point out that Claims 12, 35, 59, 67, 68, and 70 have been canceled and

so the instant objection is no longer applicable. With respect to Claim 69, the status identifier has been corrected.

Claims 49, 50, 52-57, and 60 were objected under 37 C.F.R. § 1.75(c). Claims 49, 50, 56, 57 and 60 have been canceled and so the instant objection is no longer applicable.

Claims 52-55 have been revised to correspond to revised Claims 14 and 23 to be in compliance with 37 C.F.R. § 1.75(c).

In light of the above, the objections to the claims may be properly withdrawn.

Alleged claim rejections under 35 U.S.C. § 112, second paragraph

Claims 38, 42, 49, 50, 52-57, 60-63 and 70 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 38, 42, 49, 50, 56, 57, 60-61 and 70 have been canceled and so this rejection is no longer applicable with respect to these claims.

Claims 52-55, 62 and 63 have been revised to remove references to "assaying".

In light of the foregoing, Applicants respectfully submit that this rejection has been obviated and so may be properly withdrawn.

Alleged claim rejections under 35 U.S.C. § 112, first paragraph

Claims 6-8, 10-16, 18-25, 27-38, 42, 49, 50, 52-63 and 67-70 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing "new matter". Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of "new matter" is present. Reconsideration and withdrawal of the instant rejection is respectfully requested.

With respect to the concerns based on the term "average ratio", Applicants respectfully point out that the specification and figures of U.S. Patent 7,504,214 support the term as explained below. Applicants direct the Office's attention in particular to Examples 3 and 4 as well as Figures 3, 6, and 7 in the issued patent.

For example, Tables 4 and 5 in Example 3 include identification of the 'mean' expression levels of HoxB13 and IL17BR sequences in "sections" and "LCM" samples from tamoxifen responders and non-responders. The expression level data from these "sections" and "LCM" samples for each of HoxB13 and IL17BR were scaled and plotted as values in Figure 3, which presents the value for each of the samples from both tamoxifen responders and non-responders. Applicants point out that Tables 4 and 5 of the issued patent are identical to Tables 2 and 3 of the instant application.

In Figure 3 of the patent, the data is presented in relation the scaled mean (or average) value for both responders (R) and non-responders (NR), where the mean is represented by the $\log_2$ value of "0" on the vertical axis of each graph. The value of 2^0 corresponds to 1 (one), and this same presentation format is used in Figure 6 (top panels) of the patent in relation to tamoxifen responsiveness in FFPE (formalin fixed paraffin embedded) samples. The value of 1 (one) facilitates the comparison of the data between responders and non-responders as well as comparison of expression levels between genes as discussed in Example 4 and Figure 7 of the patent.

Example 4 (see for example, column 64, line 63, to column 65, line 3, of the patent) describes using values from Figure 3 to produce a ratio, of each scaled value for HoxB13 expression over the scaled value for IL17BR expression, for each sample. The plot of these ratios is shown in Figure 7 (left panels) of the patent, wherein the mean (or average) value of 1 (one) for each of HoxB13 and IL17BR expression was used to calculate the mean (or average) ratio. A 1:1 ratio (from average HoxB13 expression over average IL17BR expression) gives a value of 1, which corresponds to the "0" value on the vertical axis in Figure 7. The use of scaled

values above and below the mean (average) value (which is "0" on the plots in Figures 3, 6, and 7) provides a common point of reference for comparison of expression levels.

In light of the foregoing, Applicants respectfully submit that there is no issue of "new matter" regarding a mean (or average) ratio as featured in the claims. So Applicants respectfully submit that no *prima facie* case of "new matter" is present, and this rejection may be properly withdrawn.

Claims 6-8, 10-16, 18-25, 27-38, 42, 49, 50, 52-63, 68 and 70 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to be supported by an enabling description. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of non-enablement is present. Reconsideration and withdrawal of the instant rejection is respectfully requested.

The pending Claims have been revised to feature methods related to aromatase inhibitors and to address concerns found in the statement of the instant rejection. As disclosed at paragraphs [0009] and [0040] of the instant application (as published in US 2005/0239083), aromatase and aromatase inhibitors in relation to ER+ breast cancer treatment are recognized and definite concepts to the skilled person. For example, aromatase is an enzyme that provides a major source of estrogen in body tissues including the breast, and aromatase inhibitors are believed to function to reduce estrogen levels in a manner comparable to tamoxifen and other "antiestrogen" agents.

Aromatase inhibitors are sufficient well known to be classified as either nonsteroidal or steroidal agents. Examples of nonsteroidal agents, which inhibit aromatase via its heme prosthetic group) include anastrozole (arimidex), letrozole (femara), and vorozole (rivisor). And examples of steroidal AIs, which inactivate aromatase, include exemestane (aromasin), androstenedione, and formestane (lentaron).

Additionally, and in the interest of improving understanding of the disclosed invention and the pending claims, Applicants present the following information regarding the

ratio of HoxB13 to IL17BR mRNA expression levels and responsiveness of ER+ breast cancer to letrozole, an aromatase inhibitor that is used against the cancer.

A study was conducted using letrozole in patients with estrogen receptor-positive (ER+) breast cancer. Needle core biopsies from newly diagnosed, untreated patients with ER+ breast cancer were taken at baseline and day 15. Patients had palpable tumors of >2 cm in diameter. Taqman RT-PCR was performed on RNA samples from the biopsies at bioTheranostics, San Diego, CA. Evaluable PCR/expression data were obtained from 47 pre-treatment samples and 53 post 15-day treatment samples. Primary endpoint was antiproliferative response defined as ln[Ki67] < 1 on day 15 in the samples analyzed.

Figure A below shows a plot of the HoxB13 to IL17BR ("H:I") expression levels (y-axis) in comparison to the antiproliferative response to letrozole (x-axis, where "0" represents non-responders and "1" represents responders). The P value is from two-sample Wilcoxon rank sum test.

Figure A

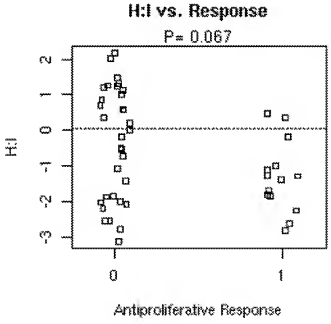

Figure A is analogous to Figure 7, left panels, in U.S. Patent 7,504,214 (properly incorporated by reference in the instant application) in presenting the H:I ratio in relation to the average H:I (a value of "0" on the y-axis) of all the samples that were assayed. The data demonstrate that a ratio of H:I that is above the average value can be used to predict, with a reasonable level of predictability, the lack of antiproliferative effect (or a lack of responsiveness) after treatment with letrozole.

In light of the foregoing, Applicants respectfully submit that no issue of non-enablement is present against the pending claims, and this rejection may be properly withdrawn.

Claims 6-38, 42, 49, 50, 52-63, and 67-70 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to be supported by an adequate written description. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of an inadequate written description is present. Reconsideration and withdrawal of the instant rejection is respectfully requested.

The revisions to independent claims 14 and 23 have been explained above. The revisions include features related to aromatase inhibitors in the claimed methods. Applicants respectfully submit there is clearly adequate description of practicing the claimed methods in relation to using an aromatase inhibitor as an antiestrogen agent (like tamoxifen as exemplified in the examples of the instant application). For example, paragraph [0040] of the instant application (as published in US 2005/0239083) clearly discloses aromatase inhibitors as embodiments of antiestrogen agents in the practice of the disclosed invention.

To the extent that the instant rejection is based upon the lack of working examples beyond adjuvant tamoxifen therapy (paragraph bridging pages 21 and 22 of the Office Action mailed February 22, 2010), Applicants respectfully point out that there is no requirement in U.S. patent law for working examples to satisfy the requirement for an adequate written description.

In light of the above, Applicants respectfully submit that no *prima facie* case is present, and this rejection may be properly withdrawn.

Alleged provisional rejections based on nonstatutory obviousness-type double patenting

Claims 6-8, 10-16, 18-25, 27-38, 42, 49, 50, 52-63, and 67-70 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 1-43 of U.S. Patent 7,504,214 B2. The basis of this rejection is that the methods in the claims of the issued patent are "a species" of the methods in the instant claims.

Applicants respectfully submit that the revised claims (related to letrozole responsiveness) no longer encompass the claims of the issued patent (related to tamoxifen responsiveness). Additionally, there is no evidence of record to support an assertion of the claims of the issued patent as rendering the instant claims obvious. And while Applicants disagree with the rejections of record in the instant application alleging lack of enablement and lack of an adequate written description, Applicants respectfully point out that statements in these rejections are inconsistent with an assertion that knowledge regarding the H:I ratio and tamoxifen responsiveness (like that in the claims of the patent) renders the instant claims obvious.

Accordingly, Applicants submit that no issue of obviousness-type double patenting is present with respect to the instant claims and those of the issued patent. Accordingly, this rejection may be properly withdrawn.

Claims 6-8, 10-16, 18-25, 27-38, 42, 58-63, and 67-70 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 1 and 9-27 of co-pending application no. 11/089,097. The basis of this

provisional rejection is that the claims of the co-pending application "recite all of the limitations" in the instant claims.

Applicants respectfully submit that the revised claims (related to letrozole responsiveness) no longer recite the same features as the claims of the co-pending application (related to tamoxifen responsiveness). Additionally, there is no evidence of record to support an assertion of the claims of the co-pending application as rendering the instant claims obvious. And while Applicants disagree with the rejections of record in the instant application alleging lack of enablement and lack of an adequate written description, Applicants respectfully point out that statements in these rejections are inconsistent with an assertion that knowledge regarding the H:I ratio and tamoxifen responsiveness (like that in the claims of the co-pending application) renders the instant claims obvious.

Accordingly, Applicants submit that no issue of obviousness-type double patenting is present with respect to the instant claims and those of the issued patent. But should this *provisional* rejection be maintained despite the above, Applicants expressly reserve the right to submit a Terminal Disclaimer to obviate this rejection.

Claims 6-8, 10-16, 18-25, 27-38, 42, 58-63, and 67-70 have been alleged to be "not patentably distinct" from Claims 1 and 9-27 in co-pending application no. 11/089,097.

Copending U.S. patent application 11/089,097 cannot qualify as prior art under any of 35 U.S.C. § 102(e), (f), or (g) in relation to the instant application. Both sections 102(e) and 102(g)(2) require an earlier invention "by another". This requirement is not met in the instant situation of identical inventorship between the copending application and the instant application. As for section 102(f), the identical inventorship between the copending application and the instant application provides no basis to allege that the instant inventors "did not ... invent the subject matter sought to be patented".

In light of the foregoing, Applicants respectfully submit that this rejection is misplaced and may be properly withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425-681-1833.

Respectfully submitted,

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